UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,255	09/17/2003	Milton G. Smith	360936-003 (ANX-001 CON)	3702

48329 7590 10/24/2006

FOLEY & LARDNER LLP
111 HUNTINGTON AVENUE
26TH FLOOR
BOSTON, MA 02199-7610

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,255	SMITH, MILTON G.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11-10-04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 8-7-06 is acknowledged.

Claims included in the prosecution are 14-39.

Double Patenting

1. The double patenting rejection is maintained in abeyance. Applicant indicates that the terminal disclaimer will be filed.

Claim Rejections - 35 USC § 112

2. Claims 14-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by 'amphipathic antioxidants' in claim 14 (also claims 21 and 27). The term, amphipathic is used in the art for a single molecule which has both hydrophilic groups and hydrophobic groups and which exhibits both attraction and repulsion to a solvent. Phospholipids for example are amphipathic. The compounds recited in claim 15 are either lipophilic or hydrophilic. Beta-carotene for example has two beta ionone rings, which are hydrophobic, and this compound is considered as a lipophilic compound. Similarly vitamin E is a lipophilic compound. The rest of the compounds recited in claim 15 are hydrophilic.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant points out to page 19, lines 8-25 of the specification, which states the following,

"Non-enzymatic antioxidants may be classified as either hydrophilic or hydrophobic. AlphaTocopherol and beta carotene are classified as hydrophobic, whereas ascorbic

acid is hydrophilic. Glutathione shares characteristics of being both hydrophilic and hydrophobic. The characteristics of being either attracted to water (hydrophilic) or being repelled by water (hydrophobic) will determine the orientation of the particular antioxidant within the cytosol and/or membrane of the cell or liposome. Therefore free radical reactions occurring in the cytosol would be quenched by either glutathione or ascorbic acid, free radicals occurring within the membrane would be quenched by alpha-tocopherol and/or beta-carotene. Each of the non-enzymatic antioxidants reacts more favorably with certain free radicals as opposed to others. For example, singlet oxygen reacts with beta-carotene; tocopherol is known to react with alkyl free radicals; glutathione and ascorbic acid are likely to be unselective in their reaction with various free radicals occurring within the cytosol".

As pointed out by the examiner and also recognized by applicant as evident from the above paragraph, the term, 'amphipathic' applies to a compound which has both hydrophobic characteristics. As recognized by applicant himself, as evident from the above paragraph, vitamin C (ascorbic acid) is hydrophilic and beta-carotene hydrophobic and neither are amphipathic. Similarly Vitamin E is hydrophobic and Niacin is hydrophilic; yet these are amphipathic according to claim 15. Furthermore, according to claim 16, one of the antioxidants is hydrophilic and the other is hydrophobic. This is inconsistent with the term, amphipathic recited in the parent claim 14. The rejection is maintained.

'said non-enzymatic antioxidants' in claim 15 lacks antecedent basis in claim 14. The term used in claim 14 is non-enzymatic, amphipathic antioxidants".

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386 and JP 62178521 (all are of record in the parent application).

Instant claims are drawn to a method of treating a disease or injury (or deleterious effects) induced by pathological free radical reactions in mammals exposed to a caustic gas by using non-enzymatic antioxidants in liposomes. The claims require a combination of two antioxidants or a combination of beta-carotene, vitamin E, glutathione and niacin.

Halliwell teaches the involvement of free radicals in a variety of human diseases. The diseases include inflammation and autoimmune diseases (pages 422-438), ischemia and reoxygenation injury (pages 438-442), cardiac injury (page 442), cerebral injury (page 444), lung damage and adult respiratory distress syndrome (pages 448-449) and cancer (pages 469-472 and 480). Halliwell also discusses the ability of anti-oxidants to react with the free radicals and protect against these radicals. The anti-oxidants taught by Halliwell include ascorbic acid (vitamin C) (page 123), glutathione (page 126), metal ions (page 131), vitamin E and carotenoids on pages 284-286.

Packer teaches interactions among antioxidants in health and disease. Packer also teaches the ability of vitamin E to quench free radicals and the synergistic action of lipid soluble and water-soluble antioxidants. Packer further teaches the diseases involving the free radicals and the effectiveness of antioxidants (note the abstract, pages 271-275).

These two references show the involvement of free radicals in various diseases and the counter acting effects of various antioxidants against the free radicals. What is lacking in Halliwell, or Packer is the specific teaching of the administration of antioxidants in liposomes. Halliwell, and Packer also lack the specific teachings of the combination of antioxidants in the treatment of free radical induced disease conditions. Halliwell and Packer are also silent with regard to the cause for the production of pathological free radicals in host system.

Woodle while disclosing liposomal formulations containing various drugs including water soluble super oxide dismutase (antioxidant) and lipophilic vitamin E (antioxidant) teaches that the liposomes are sustained release formulations and for the sustained release via the blood stream, the liposome composition is administered intravenously in an amount which provides a suitable drug dosage over the expected delivery time (note the abstract, lines 16-53 on col. 12 and claims).

Motoyama discloses synergistic inhibition of the oxidation in phosphatidylcholine liposomes by a combination of Vitamin E and cysteine; vitamin E is in the lipid bilayer and cysteine is in the aqueous compartment (note the abstract).

EP 0 455 386 teaches that the antioxidants, vitamin C and vitamin E can be encapsulated together in liposomes. Vitamin C is entrained in the aqueous layer and vitamin E in the lipid structure. EP further teaches the reasons for the inclusion of both vitamins C and E in the liposomes (note the abstract, page 2, lines 20-33).

JP 62178521 similarly teaches the encapsulation of both vitamins C and E together in liposomes. These antioxidants prevent the oxidation of hemoglobin (note the abstract).

In essence, the references of Halliwell, and Packer teach the diseases involving free radicals and the function of antioxidants in countering these free radicals. The reference of Woodle teaches that liposomes are sustained release carriers for drugs such as vitamin E (antioxidant) and the intravenous administration of the liposomes. The references of Motoyama, EP and JP teach the combination use of antioxidants and the reasons for such a combination. It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for the delivery of antioxidants to quench the free radicals involved in various diseases where free radicals are involved since liposomes are sustained delivery devices as taught by Woodle. The use of a combination of antioxidants such as vitamin C and Vitamin E together because of the references of Motoyama, EP and JP each teach that such a combination is known in the art and because of the advantages taught by Motoyama and JP. One of ordinary skill in the art would be motivated further to include combinations of antioxidants along with trace metals since UNIMED teaches the synergistic effect of combinations of anti-oxidants in sustained release preparations. Although none of the references teach the cause of the

production of the free radicals, it is deemed obvious to one of ordinary skill in the art that the anti-oxidants would nullify the effect of the free radicals irrespective of the source of the free radicals.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that there is no teaching in Halliwell and Packer for using antioxidants for reducing the damage induced by exposure to a caustic gas. This argument is not found to be persuasive since the references clearly teach the damage caused by **free radicals** and the ability of the antioxidants to protect the host against the damage caused by the free radicals. It is within the skill of the art to recognize that the antioxidants would react with the free radicals in the same way irrespective of the source of the free radicals. Applicant has not shown that the free radicals generated by caustic gas are different from those generated by other causes. Instant specification has no data showing unexpected results obtained by using just a combination of two antioxidants, which are not enzymes in host exposed to caustic gases. Applicant's arguments that the references fail to suggest the combination of antioxidants are not persuasive since Packer the ability of vitamin E to quench free radicals and the **synergistic** action of lipid soluble and water-soluble antioxidants. Packer further teaches the diseases involving the free radicals and the effectiveness of antioxidants. Applicant's arguments that the references do not teach the liposomes suitable for undergoing peroxidation and lysis are not persuasive since EP 386 teaches the use of lecithin (which has unsaturated fatty acids in the glycerol backbone) for the

formation of liposomes and indicates that unsaturated lipids undergo auto oxidation. That means the liposomes undergo lysis (liposome membranes are made of lecithin).

Applicant's arguments that Woodle does not cure the deficiencies of the Halliwell and Packer references since Woodle is directed to increasing the circulating time of a liposome encapsulated drug and demonstrating the sustained release of liposome encapsulated drugs and there is not one word in Woodle regarding a liposomal formulation with two or more antioxidants are not persuasive. Liposomes are known sustained release agents whether used by applicant or others. Woodle teaches the use of the same lecithin (see col. 13, lines 45-48) in the liposomes and suggest the encapsulation of lipophilic antioxidants such as vitamin E and hydrophilic antioxidants and the goal in Woodle is to prolong the circulation time of the liposomes without premature lysis when administered intravenously. In order to release the encapsulated active agents, the liposomes have to lyse and lysis of the liposomes would occur the same way as in instant liposomes. Instant claims do not recite any time units and the mode of administration.

Applicant argues that EP relates to fat-based food products, and particularly to a problem encountered in fat systems in cream-filled biscuits are not persuasive since, EP is teaches the encapsulation of both fat soluble and water soluble antioxidants in liposomes. Applicant argues that JP fails to disclose amphipathic antioxidant compositions of liposomes suitable for undergoing peroxidation and lysis, and the use of such for amphipathic antioxidant compositions for reducing the damage induced by the exposure to caustic gas. These arguments are not persuasive since this reference is

combined for its teachings of knowledge in the art for the encapsulation of both fat-soluble and water soluble antioxidants within the liposomes.

5. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386, JP 62178521 as set forth above, further in view of UNIMED (also of record in the parent application).

The teachings of Halliwell, Packer, Woodle, EP and JP have been discussed above.

UNIMED's advertisement on ONDROX teaches that antioxidants protect against free-radical damage; UNIMED's advertisement also shows the availability of mixtures of several antioxidants in an encapsulated form for sustained release. UNIMED teaches that the amounts of the antioxidants are theoretically synergistic; UNIMED also teaches trace metals in the combination (note the entire advertisement). UNIMED on cover page also teaches the reasons for the administration of antioxidants. One of ordinary skill in the art would be further motivated to include a combination of anti-oxidants to quench the free radicals since a synergistic effect is taught by UNIMED.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Halliwell, Packer, Woodle, EP and JP have been addressed above. Applicant argues that UNIMED discloses ONDROX, which is not a drug, but a nutritional supplement and a skilled artisan would not expect that UNIMED would produce a reduction of the deleterious effects of in a mammal exposed

to a caustic gas. These arguments are not persuasive since UNIMED is combined for its teachings of synergistic effect of antioxidants on free radicals and this effect would be the same whether they are released immediately or in a sustained release manner. Applicant has not shown to be otherwise.

6. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386, JP 62178521 and UNIMED (all are of record), further in view of either Lichtenberger (5,032,585) or Demopoulos (5,326,757) also of record in the parent application.

The teachings of Halliwell, Packer, Woodle, EP, JP and UNIMED have been discussed above.

Lichtenberger while disclosing methods for surfactant replacement therapy using lipid compositions teaches that the addition of *both* lipid and water soluble vitamins (vitamin A, E and C) and other chemical anti-oxidants with the capability of scavenging free radicals can further enhance and prolong the anti-ulcer efficacy of the lipid mixtures, and this is likely because of their ability to prevent the oxidative destruction of unsaturated phospholipids (note the abstract and col. 8, lines 22-29). Lichtenberger further teaches the encapsulation of the components in liposomes (col. 8, line 39 et seq., col. 22, line 34 et seq.).

Demopoulos while disclosing prevention and treatment of restinosis following angioplasty teaches that the administration of both water soluble and fat soluble

antioxidants with significantly reduce the radicals, particularly in tissue directly affected during angioplasty (note the abstract, col. 4, line 66 through col. 6. Line 40, examples and claims).

One of ordinary skill in the art would have been further motivated to included both lipophilic and hydrophilic antioxidants in the liposomal compositions to quench the free radicals involved in various diseases including those caused by caustic gases where free radicals are involved since Lichtenberger teaches the use of both types of antioxidants together and Demopoulos teaches the effectiveness of the combination of the antioxidants when administered together in the treatment of restinosis. The examiner also points out that combining two agents serving the same purpose would have been obvious to one of ordinary skill in the art with the expectation of obtaining at least an additive effect (see In re Kerhoven 205 USPQ 1069).

Applicant provides no specific arguments with regard to EP and JP references.

Applicant's arguments based on the declarations submitted by Dr. Smith in the parent case are not persuasive. Applicant argues that the declarations provide in vivo data showing the ability of several different amphipathic antioxidants compositions were effective in reducing the acute lung injury induced by the monofunctional analog of mustard gas. This argument is not persuasive since the results are not commensurate in scope with the scope of the claims in terms of the terms, 'caustic gas', organs affected and the anti-oxidant combination. Furthermore, the results appear to indicate an additive effect rather than an unexpected synergistic effect as seen from the values

in the Table in the declaration. The statistical significance is also unclear from the values presented in the Table.

Claims 24-26 and 37-39 are allowable once the terminal disclaimer is filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615